REMARKS

I. Status of the Specification

The specification has been amended to correct for formal defects. No new matter has been added by way of these amendments.

II. Status of the Claims

Claims 1, 2, and 4-15 were pending in the application. Claims 14 and 15 had been previously withdrawn from consideration. Claims 1, 2, and 4-13 were examined in the December 30, 2005 final Office Action. In this reply, claims 1, 6, 7, 14 and 15 have been amended for clarity. Accordingly, claims 1, 2, and 4-15 will be pending upon entry of this amendment.

Specifically, claim 1 has been amended to clarify that the method for inducing T-cell tolerance or non-responsiveness is "antigen-specific". Support for the amendments to claims 6 and 7 can be found in the specification at p. 8, ll. 28-29. Further support for the amendment to claim 7 can be found in the specification at p. 12, ll. 2-3 (Example 4), p. 15, fn. 1 (Table 1), and Figures 1, 2A and 2B.

III. Rejection Under 35 U.S.C. § 112, ¶ 1 – Written Description

The Examiner maintained rejection of claims 1, 2, 4-11 and 13 under 35 U.S.C. § 112, ¶ 1 for allegedly lacking written description support for claim 1 step (i) "purifying CD4+ T-cells from donor tissue" as well as steps (i) and (iii)-(vi) recited in claim 1, as these read on "purified donor CD4+ T-cells/T-cell tolerance". The Examiner alleges that the specification does not contain "sufficient blazemarks" for the claimed method (Office Action, dated December 30, 2005, p. 3, ¶ 3). The Examiner reasons that Applicant's reliance on Examples 1, 2 and 5 in the Amendment dated September 23, 2005 is insufficient as these Examples do not provide observations concerning the purification and administration of purified CD4+ T-cells. Specifically, the Examiner alleges that the

specification does not provide adequate written description to support the claim term of claim 1 step (i) "purified donor CD4+ T-cells" (from a donor) as these are used to induce T-cell tolerance in the donor cells as set forth in claim 1 steps (iii)-(vi).

Applicant traverses this rejection. Applicant respectfully submits that support for the rejected claim terms is found in the specification. For example, "purifying CD4+ T-cells from donor tissue" as used in claim 1 step (i) is supported by language in the specification, at p. 10, ll. 26-28, detailing the use of "highly purified CD4+ lymph node T-cells" (Example 1). Specific support is found in the specification for claim 1 steps: (iii) at p. 4, ll. 28-30, p. 7, ll. 7-10, and p. 8, ll. 6-9 and l. 24; (iv) at pp. 4-5, ll. 30-1; (v) at p. 4, ll. 24-27 and p. 8, ll. 27-28; and (vi) at p. 9, ll. 1-2, pp. 10-13, ll. 26-10; and Figures 1-4B. Additionally, claim 1 steps (iii)-(v), taken collectively, are supported in the specification at p. 8, ll. 22-29.

The Examiner further alleged lack of written description for the phrase "for a time ranging from about 5 to 30 days" recited in claim 6 and "for a time ranging from 6 to 10 days" recited in claim 7. The Examiner specifically contends that Applicant relies on a generic disclosure regarding time that does not support the claimed species of "5 to 30" days in claim 6 and "from 6 to 10" days in claim 7.

To expedite prosecution, without conceding the correctness of this rejection, claims 6 and 7 have been amended herein to more closely reflect the language provided in the specification at p. 8, ll. 28-29, which recites "[t]ypically, this time will range from about 1-2 days to 30 days, more typically about 5-15 days, and most typically about 10 days", thereby obviating this rejection.

In view of the foregoing, it is respectfully submitted that the written description rejection has been obviated or overcome. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Rejection Under 35 U.S.C. § 103

The Examiner maintained his rejection of claims 1, 2, 4-11 and 13 under 35 U.S.C. § 103(a) as allegedly obvious over Noelle (Noelle) (U.S. Patent No. 5,876,718), in view of Rooney et al.

(Rooney) (U.S. Patent No. 5,962,318), and in view of Riddell et al. (Riddell) (J. Immunol. Methods 128: 189-201) and Sykes et al. (Sykes) (U.S. Patent No. 6,006,752), and in further view of Ochoa et al. (Ochoa) (U.S. Patent No. 5,725,855) and Knulst et al. (Knulst) (Eur. J. Immunol. 23: 299-302, 1993). The Examiner notes that the Ochoa and Knulst references were specifically added in response to the Amendment dated September 23, 2005 which he alleges read on "purification and administrating [sic] purified CD4+ T-cells per se in transplantation regimes." Office Action, dated December 30, 2005, p. 3, ¶ 6.

Summary of the Examiner's Rejections in relation to each of the six references:

(A) **Noelle**: The Examiner alleges that Noelle teaches that: (1) CD4+ T-cells are required for the induction of CTL formation; (2) anti-gp39 antibodies may induce allospecific tolerance in both the CD4+ and CD8 T-cell compartments of the immune system and that this may be obvious beneficial therapeutic intervention when considering transplant immunology and immunotherapy; (3) the reactivity of anti-gp39 antibodies on T-cells, including CD4+ T-cells; (4) the isolation and *ex vivo* treatment of bone marrow cells; (5) *in vivo* administration of anti-gp39 antibodies; (6) depleting T-cells from antigen presenting cells; (7) methods to tolerize T-cells in vitro with a gp39 antagonist to affect contact dependent helper effector function; that is, inducing T-cell non-responsiveness to desired alloantigens with gp39 antagonists including the use of anti-gp39 antibodies and antigen presenting cells; and (8) various assays to monitor the induction of T-cell tolerance.

The Examiner concedes that Noelle does not teach: (1) the purification and (2) testing of isolated CD4+ T-cells in a (3) mixed lymphocyte reaction (MLR) under the claimed conditions.[1] Noelle also does not teach the time ranges specified in claims 6 and 7.

(B) **Rooney:** The Examiner alleges that Rooney teaches: (1) the irradiation of antigen presenting cells to alleviate the activity of other cell types including T-cells given that antigen presentation was still provided; and (2) that effector cells can be helper CD4+ T-cells as well as cytotoxic CD8+ T-cells which can be administered for cellular immunotherapy.

[1] The Examiner acknowledges that Noelle "does not mention mixed lymphocyte reaction per se," he nonetheless argues that "it would have readily apparent to the one of ordinary skill in the art at the time the invention was made that a mixed lymphocyte reaction was accomplished by carrying out" the method disclosed therein. Office Action, dated December 30, 2005, pp. 5-6, ¶¶ 8-1.

The Examiner concedes that Rooney was provided as *background* to address some basic principles and practices of cell culture and manipulation in the art at the time of invention.

(C) **Ochoa (newly added):** The Examiner alleges that Ochoa teaches the manipulation of immune cell subsets, including CD4+ T-cells as well as CD8+ T-cells *ex vivo* prior to administration in various therapeutic regimens.

(D) **Riddell:** The Examiner alleges that Riddell teaches cloning and expanding human antigen-specific T-cells, including CD4+ T-cells as well as CD8+ T-cells *ex vivo* over various lengths of time (for up to three months) prior to administration in various therapeutic regimes.

The Examiner concedes that Riddell was not relied upon for teaching adoptive transfer of T-cells to induce an immune response in transplant recipients.[2]

(E) **Knulst (newly added):** The Examiner alleges that Knulst teaches the principle role of CD4+ T-cells in GVHD and the advantages of treating or inhibiting said CD4+ T-cells in decreasing morbidity and increasing survival in GVHD patients.

(F) **Sykes:** The Examiner alleges that Sykes teaches: (1) monitoring the induction of T-cell non-responsive *ex vivo*; that is, that putative immunosuppressive agents can be prescreened by *in vitro* or *in vivo* tests/assays, including those for transplantation by assessing of the ability of a treated T-cell to release a cytokine to determine the effect of an immunosuppressive drug.

Adding to the prior arguments of record, the Examiner newly argues that the references teach irradiating antigen-presenting cells for *ex vivo* stimulation.[3]

The Examiner additionally contends that the Applicant has not satisfied their burden of proof that the invention is not *prima facie* obvious. Specifically, the Examiner contends that references cannot be argued individually (*In re Young*, 403 F.2d 759 (CCPA 1968); *see* MPEP § 2145). The Examiner contends that the combination of references is proper based on the teachings of Noelle coupled with the teachings of the secondary references in providing well-established culture

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[2] Office Action, dated December 30, 2005, p. 6, ¶ 3.

[3] However, the Examiner concedes that "[t]he secondary references simply filled in well-practiced and established methods of manipulating and testing immune cells, particularly T-cell antigen presenting cell interactions. [and that there] is no discouragement nor skepticism in the prior art for the *ex vivo* manipulation of donor and recpieint [sic] cell population to achieve antigen specific non-responsiveness in transplantation regiments at the time the invention was made." Office Action, dated December 30, 2005, p. 7, ¶ 9).

conditions and methods of manipulation involving specific cell interactions and end points where such a combination gives rise to a reasonable expectation that some advantage or expected beneficial result would be produced upon combination (*In re Sernaker*, 17 USPQ 1, 5-6 (Fed. Cir. 1983); *see* MPEP § 2144). Additionally, the Examiner acknowledges that there must be some teaching, suggestion or motivation to combine the references, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (*In re Fine*, 5 USPQ 1596 (Fed. Cir. 1988), *In re Jones*, 21 USPQ 1941 (Fed. Cir. 1992)), and that the test is whether these combined teachings would have suggested the invention to one of ordinary skill in the art (*In re Keller*, 642 F.2D 413 (CCPA 1981); *see* MPEP § 2145).

Applicant respectfully traverses this rejection.

The present invention provides a successful method for treating donor T-cells *ex vivo*, to render such T-cells substantially non-responsive to recipient antigens. The disclosure of the invention describes a method for treating donor T-cells *ex vivo* with a gp39 (CD154) antagonist and recipient cells. The claimed method of the invention successfully renders donor T-cells substantially non-responsive to recipient antigens. The present invention thus provides an effective means of preventing or inhibiting GVHD responses that would otherwise potentially occur upon transplantation of donor tissues into a recipient.

The inventors have determined that the GVHD response can be controlled by tolerizing donor T-cells *ex vivo* in a specific manner. First, $CD4^+$ helper T-cells are removed and purified from the donor; as an additional requirement, recipient cells are irradiated to remove recipient T-cells; then the purified T-cells are incubated in a mixed lymphocyte reaction culture with the irradiated recipient cells and a gp39 antagonist. Exposure to the recipient cells in combination with the gp39 antagonist causes any donor $CD4^+$ T-cells that recognize the recipient cells as foreign to become non-responsive to recipient antigens. When treated in this manner, transplanted donor tissue does not cause a GVHD reaction in recipients.

Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.[4] As explained in detail below, the Examiner has failed to cite references that either alone, or in combination, teach all the limitations of the presently claimed invention. Specifically, the limitations of Claim 1, steps (i) and (ii), are not accounted for by the prior art. Further, there is no teaching or suggestion to combine and/or modify the cited references to arrive at the claimed invention. Also, the Examiner improperly relies on isolated portions of several references that would not have been relied on by those having ordinary skill in the art at the time of invention as the combination of references does not achieve a beneficial result by their combination. Further, several of the cited references, which must be read as a whole, teach methods with opposite results to those achieved by practice of Applicant's claims and, thus, teach away from the claimed invention. Finally, the references cited by the Examiner, taken alone or in combination, do not give rise to an expectation of success. Indeed, three of the six references achieve a result opposite to Applicant's claimed invention—*stimulation* of the immune system—and these opposite teachings would have frustrated efforts by one having ordinary skill to achieve with any certainty the claimed invention, given that modification of the gp39 mechanism is rooted in a highly unpredictable art.

Thus, Applicant respectfully submits that Examiner has failed to establish, under any of the required three foundations, a case a *prima facie* obviousness (MPEP § 2143). Arguments in connection with each foundation are set forth below.

1. The Examiner has failed to cite references that either alone, or in combination, teach all the limitations of the presently claimed invention

The cited references do not render obvious the claimed method using MLR in which purified donor CD4+ T-cells are combined with irradiated T-cell depleted recipient alloantigen-bearing cells and exposed to gp39 antagonist to induce antigen-specific immunotolerance.

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[4] § 2143 of the MPEP requires that 3 basic criteria be met to establish a *prima facie* case of obviousness: (1) the references taken alone or in combination must teach or suggest all the claimed limitations; (2) suggestion/motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings; and (3) a reasonable expectation of success.

Specifically, claim 1, steps: (i) "purifying CD4+ T-cells from donor tissue"; and (ii) "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells" are not taught or suggested by any of the cited references, either alone, or in combination. Further, absent the limitations recited in claim 1 steps (i) and (ii), the specific MLR recited in claim 1 steps (iii)-(v) and comprised of the cells as defined in steps (i) and (ii), is also not rendered obvious.

Noelle, the primary reference relied upon by the Examiner, does not teach that the donor T-cells must be purified $CD4^+$ T-cells, or that the recipient alloantigen-bearing cells or B cells are first irradiated to deplete recipient T-cells. Thus, Noelle fails to teach crucial aspects of the invention. In order for the combination of references to provide all the limitations of the claimed invention, the use of purified $CD4^+$ T-cells from a donor, and the use of recipient alloantigen-bearing cells and/or B cells, which have been irradiated to remove recipient T-cells, must be taught or suggested by Rooney, Riddell, Sykes, Ochoa, or Knulst. Applicants respectfully submit that this is not the case.

A. Claim 1, step (i): "purifying $CD4^+$ T-cells from donor tissue"

Claim 1, step (i) recites "purifying $CD4^+$ T-cells from donor tissue". Applicant submits that none of the cited references alone, or in combination, teaches or suggests the limitation of this claim step.

The Examiner concedes that **Noelle** does not teach the purification of CD4+ T-cells. Though previously argued (*see* Amendment, dated June 21, 2005), the Examiner has not accounted for this missing limitation. While the Examiner contends that Knulst teaches the principle role of CD4+ T-cells in GVHD and the advantages of treating or inhibiting said CD4+ T-cells in decreasing morbidity and increasing survival in GVHD patients, the Examiner does not rely on any particular teaching in this reference regarding purification of CD4+ T-cells from donor tissue.

Applicant submits that this missing limitation is not accounted for in any of the other prior art, taken alone or in combination. **Rooney, Ochoa, Riddell,** and **Sykes** are silent on the issue of "purifying $CD4^+$ T-cells from donor tissue." **Knulst** teaches that injections of certain blood fractions to lethally irradiated mice prior to transplant mitigate GVHD. Knulst (abstract). Knulst

does not teach or suggest *ex vivo* modification of donor cells, and, thus, does not teach or suggest "purifying CD4+ T-cells from donor tissue" in the context of claim 1, step (i), or the MLR of step (iii). Further, the "lethally irradiated" mice in Knulst do not present any alloantigen-bearing cells, let alone the T-cell depleted alloantigen-bearing cells as required in claim 1, step (ii).

B. Claim 1, step (ii): "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T- cells"

Claim 1, step (ii) recites "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T- cells". Applicant submits that none of the cited references alone, or in combination, teach or suggest the limitation of this claim step.

The Examiner states that **Noelle** teaches irradiating alloantigen-bearing cells for *ex vivo* stimulation.

However, Noelle does not teach or suggest the use of irradiation to deplete T-cells *only* from a population of alloantigen-bearing cells. Noelle merely suggests that T-cells can be depleted by treatment with anti-T-cell antibody (Noelle, column 10, lines 34-37).

The Examiner states that **Rooney** provides basic principles and practices of cell culture, including irradiation of alloantigen-bearing cells.

Applicant submits that Rooney does not teach or suggest the use of irradiation to deplete T-cells *only* from a population of alloantigen-bearing cells. Rooney teaches irradiation to deplete alloantigen-bearing cells *generally* (*see* Rooney at columns 14-15, overlapping paragraph). Rooney teaches that an alloantigen-bearing cell, or antigen presenting cell, is defined as "an immune accessory cell that participates in antigen-inductive events, and includes mononuclear phagocytes, dendritic cells, and B cells" (Rooney, cols. 10-11, ll. 66-2). Effector cells are "cells of the immune system that mount responses to protect individuals from pathogens" and encompass T-cells (Rooney, col. 11, ll. 36-42), which are cells of a lineage distinct from alloantigen-bearing cells.

The teaching of irradiation in Rooney does not suggest its use to *specifically eliminate* immunoreactive recipient T-cells, while keeping alloantigen-bearing cells and other cell types intact. One of skill in the art seeking to eliminate T-cells to suppress immunoresponse would not use the methods of Rooney to achieve that end.

Indeed, assuming for the sake of argument that the Examiner is correct in that Rooney provides the basic principles and practices known in the art in terms of manipulation of cell populations using irradiation, then Rooney provides further evidence that Applicant's different use of irradiation to remove only T-cells rather than promote their growth is, in fact, distinct from what was generally known.

The Examiner newly cites **Ochoa** contending that Ochoa teaches the manipulation of immune cell subsets, including CD4+ T-cells as well as CD8+ T-cells *ex vivo* prior to administration in various therapeutic regimens.

Applicant submits that Ochoa is silent regarding the use of irradiating a population of cells to *deplete* only CD4+ T-cells. Instead, Ochoa teaches other methods to create a "depleted immune cell population and immune cell subsets, [that] preferably develop increased immunotherapeutic activity" (Ochoa, col. 9, ll. 19-22), including the use of magnetic beads (Ochoa, Examples 1 and 3), a centrifuge (Example 2), irradiation of isolated CD4+ and CD8+ T-cells (Ochoa, Example 5), and a cell purification column (Ochoa, Examples 6, 7, 10 and 11).

Applicant submits that **Riddell** is wholly silent on the issue of irradiation to select subpopulations of cells.

Applicant submits that **Knulst** is wholly silent on the issue of irradiation to select subpopulations of cells. Further, the "lethally irradiated" mice in Knulst do not present any alloantigen-bearing cells, let alone the T-cell depleted alloantigen-bearing cells as required in claim 1, step (ii).

Applicant submits that **Sykes** is wholly silent on the issue of irradiation to select subpopulations of cells. Sykes, like Noelle, teaches that anti-T-cell antibodies lead to T-cell depletion (Sykes, col. 10, ll. 25-27).

Noelle combined with Rooney, Ochoa, and Sykes fail to teach irradiation to remove T-cells only from alloantigen-bearing cells obtained from a recipient, and Riddell and Knulst are wholly silent on this issue. Having read the teachings of Noelle, Rooney, Ochoa, and Sykes, and with the understanding that irradiation is an appropriate method to prevent proliferation of alloantigen-bearing cells (Rooney, Ochoa), while treatment with anti-T-cell antibodies and complement is an appropriate way to remove T-cells while leaving alloantigen-bearing cells intact (Noelle and Sykes), the skilled artisan seeking to eliminate T-cells would conclude that irradiation of cells would result in a cell population depleted of alloantigen-bearing cells but enriched for immunoreactive T-cells—a result *opposite* to the claimed invention. Accordingly, one of ordinary skill in the art would not irradiate recipient tissue, but rather would apply anti-T-cell antibodies to recipient tissue. Therefore, the combination of Noelle, Rooney, Ochoa, Riddell, Knulst, and Sykes cannot make obvious the use of irradiation of recipient T-cells to deplete recipient T-cells from a mixed cell population.

C. Claim 1, steps (iii)-(v)

Applicant respectfully submits that because the limitations of claim 1, steps (i) and (ii) are not taught or suggested by the cited prior art, either taken alone, or in combination, that the specific MLR comprised of purified CD4+ donor T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells recited in claim 1, steps (iii)-(v) is also not taught or suggested by the cited references. The specific use of purified donor CD4+ T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells is recited directly in claim 1, steps (iii)-(iv), and it is this particular MLR that is maintained in claim 1, step (v), in culture for a sufficient time to render the donor CD4+ T-cells substantially tolerant or non-responsive to the irradiated T-cell depleted alloantigen-bearing recipient cells. Accordingly, the missing limitations in claim 1, steps (i) and (ii) likewise render the MLR of claim 1 steps (iii)-(v) nonobvious over the cited prior art.

2. There is no suggestion or motivation to modify the references or combine reference teachings

The Examiner asserts that legal precedent supports his argument that he has established a *prima facie* case of obviousness based on the combination of the selected prior art. However, Applicant respectfully submits that he has made improper use of the prior art, particularly in his reliance on Riddell, Rooney, and Ochoa. Accordingly, these references should be removed from consideration in relation to the pending application. As discussed below, this argument has two foundations.

First, the Examiner uses the benefit of hindsight and improperly picks and chooses references that would not have been combined by artisans of ordinary skill in the art at the time of invention. It is our position that, at the time of invention, *activation* of the immune system via the gp39 mechanism was better understood than its *deactivation*, let alone the claimed induction of antigen-specific immunotolerance which can be based, in part, on the same mechanism. Just because activation of an immune response via the gp39 pathway may have been known at the time of invention, such knowledge certainly would not lead one of ordinary skill in the art to rely on references teaching *activation* via the gp39 pathway to attempt to accomplish its effective *deactivation*. At the time of invention it was understood that this art was *highly unpredictable*. Accordingly, the Examiner's presumption that one would have considered the gp39 pathway as a simple on/off switch and would just as soon turn to references teaching its activation as its deactivation underestimates the upredictability in this art.

Second, and further to the first, three of cited references teach away from the claimed invention in that they disclose methods leading to *enhanced activation* of the immune system—an opposite result to *immunotolerance*. These arguments have solid footing in the law.

35 U.S.C. § 103 requires assessment of the invention as a whole such that the Examiner must show that an artisan of ordinary skill in the art at the time of invention, confronted by the same

problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner (*Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1375 (Fed. Cir. 2000)). References must be considered for all that they teach, and may not be applied out of their own context to render a claimed invention obvious absent any suggestion to do so (*see id.* 1371-72). Indeed, the Examiner's selection of references is impermissible because he has used the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious (*In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (citing *In re Fine,* 837 F.2d 1071, 1075 (Fed. Cir. 1988)). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *Id.*

The Examiner argues that there "is no discouragement nor skepticism" regarding the proposed combination of references (Office Action, dated December 30, 2005, p. 7, ¶ 9). Applicant submits that here the Examiner applies the wrong standard for determining whether a particular selection of references might be combined to support a finding of obviousness and, further, that under the correct standard, at least Rooney, Riddell, and Ochoa teach away from the presently claimed invention because they teach *enhancing activation* of the immune response.

It is understood that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant" (*Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)); *see In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966) (stating that a reference which teaches an opposite concept teaches away, and cannot be properly combined to make an obviousness rejection)). Importantly, here the Applicant seeks a result of *induced immunological tolerance*—a result opposite to Rooney, Riddell, and Ochoa's teaching of *enhanced immunological response*. In fact, the Examiner concedes Riddell and Rooney (like newly cited Ochoa) may use T-cells to accomplish different endpoints, i.e., enhanced vs. tolerized immune response (Office Action, dated December 30, 2005, p. 6, ¶¶ 4 and 8). Thus, not only would one having ordinary skill in the art at the time of invention *not* have relied on these

references, these references, in fact, teach away from the claimed method because they disclose methods producing opposite results in a highly unpredictable art. Indeed, *Applicant submits that the growth and expansion of antigen-specific T-cells is the central problem in GVHD* for which the present invention can be used to circumvent.

Rooney seeks to *stimulate* an immune response to specific antigens for adoptive transfer, which is useful to treat infections in immunocompromised individuals, or to treat tumors (Amendment, dated June 21, 2005, pp. 11-12, ¶4-1; that is, "[i]rradiation of APCs [alloantigen-bearing cells] prevents their [alloantigen-bearing cells] proliferation, thus ensuring that only antigen-specific effector cells [e.g., T-cells] are selected in the culture" (*see* Rooney, cols. 14-15, ¶¶ 4-1, *see also* Abstract, stating that "[t]he present invention is directed to methods of stimulating primary and secondary effector cell responses for cellular immunotherapy"). The Examiner acknowledges that Riddell similarly teaches "expanding human antigen-specific T-cells" (Office Action dated December, 30 2005, p. 4, ¶ 5).[5] The newly cited Ochoa reference also teaches *enhancement* of an immune response such that "populations rapidly develop and maintain high levels of NK [natural killer] and LAK [lymphokine activated killer] activity" Ochoa, col. 17, ll. 21-22.[6]

3. There is no reasonable expectation of success

There is no teaching or suggestion in the prior art regarding the claimed features in claim 1, steps (i) and (ii). Further, assuming arguendo that the cited references are properly cited, the Examiner has presented a combination of references that provide no reasonable expectation of success for achieving the claimed invention (see, teaching away discussion above). Indeed, half of the cited references, Rooney, Riddell, and Ochoa, result in *enhanced* immunoactivation—not

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[5] The method of culturing T-cells taught in Riddell involves collecting peripheral blood mononuclear cells and treating these cells in a mixed lymphocyte reaction (MLR) culture with antibodies to stimulate the growth of T-cells that are responsive to antigen. Application of anti-CD3 and anti-CD28 monoclonal antibodies to blood cells leads to expansion of T-cell populations. Riddell further teaches that culturing cells with anti-CD3 antibodies leads to cell populations which are *enriched* for alloreactive T-cells (Riddell, *see* p. 192, col. 2, ¶ 1).

[6] The method of Ochoa is used for treatment of tumors and generation of bone marrow cells using T-cell subpopulations cultured in the presence of antibodies, and optionally in the presence of cytokines.

immunotolerance. Accordingly, Rooney, Riddell, and Ochoa teach away from the claimed invention.

One of ordinary skill in the art at the time of invention would not have been prompted by any combination of the cited prior art and/or their own knowledge to create the claimed method using an MLR comprising purified donor CD4+ T-cells, irradiated, T-cell depleted recipient alloantigen-bearing cells, and a gp39 antagonist to induce immunotolerance or non-responsiveness in the donor CD4+ cells. This is particularly the case where certain elements of the claimed method do not appear in any context in the cited prior art.

In view of the foregoing, it is respectfully submitted that the obviousness rejection has been overcome. Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes the pending application is in condition for allowance. Favorable action is respectfully requested. In the event that any issue remains in connection herewith, the Examiner is respectfully invited to contact the undersigned to discuss the same.

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